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Term: non-CpG

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DATE: Wednesday, July 31, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L4	l2 with l1	1	L4
L3	Th2	3487	L3
L2	immunostimulat$	3829	L2
L1	non-CpG	19	L1

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L4: Entry 1 of 1 File: PGPB Nov 22, 2001

PGPUB-DOCUMENT-NUMBER: 20010044416
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010044416 A1

TITLE: Immunostimulatory nucleic acids for inducing a Th2 immune response

PUBLICATION-DATE: November 22, 2001

US-CL-CURRENT: 514/44; 514/110, 514/179, 514/9

APPL-NO: 09/ 768012 [PALM]
DATE FILED: January 22, 2001

RELATED-US-APPL-DATA: *** TEST ***
Application is a non-provisional-of-provisional application 60/177461, filed January 20, 2000,

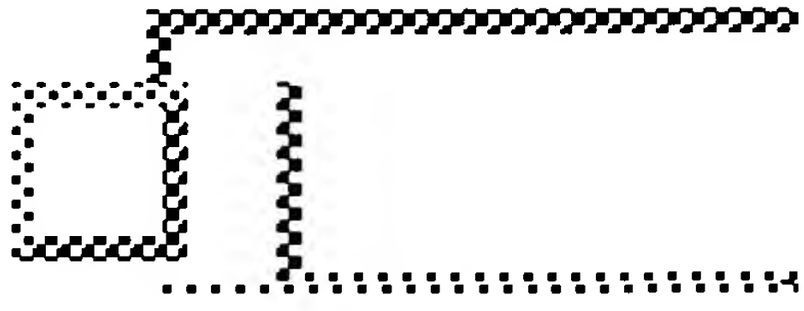
L1: Entry 8 of 19 File: USPT

DOCUMENT-IDENTIFIER: US 6406705 B1
TITLE: Use of nucleic acids containing unmethylated CpG dinucleotide as an adjuvant

Brief Summary Text (27):
FIG. 3 is a graph illustrating humoral responses in adult BALB/c mice immunized with 1 .mu.g recombinant HBsAg protein, with or without alum, and with one of several different oligonucleotides (ODN, 10 .mu.g). The ODN were made with a natural phosphodiester backbone (O), synthetic phosphorothioate backbone (S) or a chimeric of phosphodiester center regions and phosphorothioate ends (SOS). Most of the ODN contained 1-3 CpG motifs but some of the ODN were non-CpG controls (1911, 1982, 2041). Each point represents the group mean (n=5) for anti-HBs titers (total IgG) as determined by end-point dilution ELISA assay.

Detailed Description Text (133):
Other groups of mice (n=5) were immunized with HBsAg (1 .mu.g) alone, with alum (25 .mu.g A13+), with one of several different CpG and non-CpG control oligonucleotides of different backbones (10 .mu.g), or with both alum and an oligonucleotide.

Detailed Description Text (153):
When a large panel of ODN is compared for adjuvant activity it can be seen that CPG ODN with a nuclease-resistant phosphorothioate backbone have the best adjuvant effects (FIG. 3). There was very little or no adjuvant activity of non-CpG control ODN with a phosphorothioate backbone, or of CpG ODN with a chimeric or phosphodiester backbone. However, for those phosphorothioate CpG ODN that did not have adjuvant effect, all exhibited a synergistic effect with alum. In general, antibody titers with combined alum and CpG ODN were 10 to 100-fold higher than with CpG ODN and/or 100 to 1000-fold higher than with alum alone (FIG. 3).



Generate Collection Print

L1: Entry 14 of 19 File: USPT

DOCUMENT-IDENTIFIER: US 6194388 B1
TITLE: Immunomodulatory oligonucleotides

Brief Summary Text (59):
To determine whether CpG ODN can cause in vivo immune stimulation, DBA/2 mice were injected once intraperitoneally with PBS or phosphorothioate CpG or non-CpG ODN at a dose of 33 mg/kg (approximately 500 .mu.g/mouse). Pharmacokinetic studies in mice indicate that this dose of phosphorothioate gives levels of approximately 10 .mu.g/g in spleen tissue (within the effective concentration range determined from the in vitro studies described herein) for longer than twenty-four hours (Agrawal, S. et al. (1991) Proc. Natl. Acad. Sci. USA 91:7595). Spleen cells from mice were examined twenty-four hours after ODN injection for expression of B cells surface activation markers Ly-6A/E, Bla-1, and class II MHC using three color flow cytometry and for their spontaneous proliferation using .sup.3 H thymidine. Expression of all three activation markers was significantly increased in B cells from mice injected with CpG ODN, but not from mice injected with PBS or non-CpG ODN. Spontaneous .sup.3 H thymidine incorporation was increased by 2-6 fold in spleen cells from mice injected with the stimulatory ODN compared to PBS or non-CpG ODN-injected mice. After 4 days, serum IgM levels in mice injected with CpG ODN in vivo were increased by approximately 3-fold compared to controls. Consistent with the inability of these agents to activate T cells, there was minimal change in T cell expression of the IL-2R or CD-44.

Brief Summary Text (62):
As described in further detail in Example 4, experiments were conducted to determine whether CpG containing oligonucleotides stimulated the activity of natural killer (NK) cells in addition to B cells. As shown in Table 3, a marked induction of NK activity among spleen cells cultured with CpG ODN 1 and 3Db was observed. In contrast, there was relatively no induction in effectors that had been treated with non-CpG control ODN.

Brief Summary Paragraph Table (3):
TABLE 3 Induction Of NK Activity By CpG Oligodeoxynucleotides (ODN) % YAC-1 Specific Lysis* % 2C11 Specific Lysis Effector: Target Effector: Target ODN 50:1 100:1 50:1 100:1 None -1.1 -1.4 15.3 16.6 1 16.1 24.5 38.7 47.2 3Db 17.1 27.0 37.0 40.0 non-CpG ODN -1.6 -1.7 14.8 15.4

Detailed Description Text (37):
10.times.10.sup.6 C57BL/6 spleen cells were cultured in two ml RPMI (supplemented as described for Example 1) with or without 40 .mu.M CpG or non-CpG ODN for forty-eight hours. Cells were washed, and then used as effector cells in a short term .sup.51 Cr release assay with YAC-1 and 2C11, two NK sensitive target cell lines (Ballas, Z. K. et al. (1993) J. Immunol. 150:17). Effector cells were added at various concentrations to 10.sup.4 51 Cr-labeled target cells in V-bottom microtiter plates in 0.2 ml, and incubated in 5% CO.sub.2 for 4 hr. at 37.degree. C. Plates were then centrifuged, and an aliquot of the supernatant counted for radioactivity. Percent specific lysis was determined by calculating the ratio of the .sup.51 Cr released in the presence of effector cells minus the .sup.51 Cr released when the target cells are cultured alone, over the total counts released after cell lysis in 2% acetic acid minus the .sup.51 Cr cpm released when the cells are cultured alone.

Detailed Description Text (52):
Whole cell extracts from CH12.LX B cells showed 2 retarded bands when analyzed by EMSA with the CRE probe (free probe is off the bottom of the figure). The CREB/ATF protein(s) binding to the CRE were competed by the indicated amount of cold CRE, and by single-stranded CpG ODN, but not by non-CpG ODN.

(FILE 'HOME' ENTERED AT 07:35:05 ON 31 JUL 2002)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, EMBASE, BIOSIS, CAPLUS' ENTERED AT 07:35:41 ON 31 JUL 2002

L1	25986	S IMMUNOSTIMULAT?
L2	41360	S TH2
L3	730	S L2 AND L1
L4	163	S CPG AND L3
L5	63	DUP REM L4 (100 DUPLICATES REMOVED)

L5 ANSWER 59 OF 63 MEDLINE DUPLICATE 33
AN 1998233709 MEDLINE
DN 98233709 PubMed ID: 9574565
TI Cationic lipids enhance cytokine and cell influx levels in the lung following administration of plasmid: cationic lipid complexes.
AU Freimark B D; Blezinger H P; Florack V J; Nordstrom J L; Long S D; Deshpande D S; Nochumson S; Petrak K L
CS GeneMedicine, Inc., The Woodlands, TX 77381, USA.. Freimb@GeneMedicine.com
SO JOURNAL OF IMMUNOLOGY, (1998 May 1) 160 (9) 4580-6.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; AIDS
EM 199805
ED Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980521

AB Administration of plasmid/lipid complexes to the lung airways may be associated, in addition to expression of transgene, with a range of other responses. We report here the induction of cytokines and cellular influx in the lung airway following intratracheal administration of an N-[1-(2-3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride/cholesterol/plasmid positively charged complex in mice. We show that 1) the appearance of the Th1-associated cytokines IFN-gamma and IL-12 in bronchoalveolar lavage fluid is caused by unmethylated **CpG** dinucleotide sequences present within the plasmid, and is enhanced by the lipid formulation; 2) cationic lipids by themselves do not induce IL-12 or IL-12p40; 3) TNF-alpha is rapidly induced by cationic lipids and plasmid/lipid complex, but not by plasmid alone; 4) an acute cellular influx is induced by cationic lipid alone and by a plasmid/lipid complex, but to a much lesser extent by plasmid alone; and 5) plasmid methylation does not influence the degree of inflammatory cell influx. The induction of the innate immune responses by plasmid/lipid complexes may be advantageous to gene therapy of lung diseases. In particular, induction of the Th1 cell-promoting cytokines by plasmid/lipid complexes could, in conjunction with an expressed transgene, be used to modulate immune responses in the lung airways in disease conditions that are deficient in Th1 cell responses or that have a dominant **Th2** phenotype. Alternatively, the elimination of **immunostimulatory** sequences in plasmids may improve the tolerability and/or efficacy of nonviral gene therapy, especially for diseases requiring chronic administration.

L5 ANSWER 57 OF 63 CAPLUS COPYRIGHT 2002 ACS
AN 1998:293516 CAPLUS
DN 129:23430
TI **Immunostimulatory** nucleic acid molecules
IN Krieg, Arthur M.; Kline, Joel N.
PA University of Iowa Research Foundation, USA; Krieg, Arthur M.; Kline, Joel N.
SO PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9818810	A1	19980507	WO 1997-US19791	19971030
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6207646	B1	20010327	US 1996-738652	19961030
	AU 9852424	A1	19980522	AU 1998-52424	19971030
	EP 948510	A1	19991013	EP 1997-947311	19971030
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1235609	A	19991117	CN 1997-199352	19971030
	JP 2001503267	T2	20010313	JP 1998-520784	19971030
	KR 2000052994	A	20000825	KR 1999-703873	19990430
PRAI	US 1996-738652	A2	19961030		
	US 1994-276358	B2	19940715		
	US 1995-386063	A1	19950207		
	WO 1997-US19791	W	19971030		

OS MARPAT 129:23430
AB Nucleic acid sequences contg. unmethylated **CpG** dinucleotides that modulate an immune response including stimulating a Th1 pattern of immune activation, cytokine prodn., NK lytic activity, and B cell proliferation, are disclosed. The sequences are also useful as synthetic adjuvants.

L5 ANSWER 55 OF 63 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999107639 EMBASE
TI Inhibition of allergic inflammation in the lung by plasmid DNA allergen immunization.
AU Spiegelberg H.L.; Broide D.; Tighe H.; Roman M.; Raz E.
CS Dr. H.L. Spiegelberg, Div. of Pediatric Immunology/Allergy, Department of Pediatrics 0833, UCSD School of Medicine, San Diego, CA 92093-0833, United States. hansspiege@aol.com
SO Pediatric Pulmonology, (1999) 27/SUPPL. 18 (118-121).
Refs: 15
ISSN: 8755-6863 CODEN: PEPUES
CY United States
DT Journal; Conference Article
FS 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB The nature of the immune response (Th1/**Th2**) in mice to protein antigens or allergens was compared to that of immunization with pDNA encoding the same antigens. pDNA immunization induced a Th1 response and no IgE antibodies whereas the proteins induced a **Th2** response and IgE antibodies. Furthermore, the pDNA induced Th1 response dominated over the protein elicited **Th2** response in a secondary immune response. In particular, a preexisting **Th2** response (as is the case in allergic patients) did not prevent a new Th1 response to an allergen-pDNA booster injection. The major reason why pDNA immunization induced a Th1 response to allergens was the presence of **immunostimulatory** non-coding DNA sequences (ISS) in the plasmid constructs having a **CpG** motif. These ISS caused antigen presenting cells to secrete INF- .alpha., INF-.beta. and IL-12, all cytokines that induce naive T cells to differentiate into CD4+ Th1 cells and CD8+ Tc1 cells. Passive transfer of both Th1 and Tc1 cells from pDNA immunized mice into naive mice inhibited a **Th2** response and IgE antibody formation to a subsequent injection of allergen in alum. pDNA immunization or ISS-oligonucleotide injection prior to allergen challenge reduced both immediate type airway sensitivity and late phase allergen induced eosinophil infiltration of the lung. Allergen-pDNA immunization may provide a novel type of immunotherapy for the treatment of allergic diseases in man. Since only small amounts of allergen are secreted by the allergen-pDNA transformed cells, allergen-pDNA immunotherapy will unlikely carry the risk of the anaphylactic reactions that are associated with classical allergen injection immunotherapy.

L5 ANSWER 53 OF 63 MEDLINE DUPLICATE 30
AN 2000013319 MEDLINE
DN 20013319 PubMed ID: 10544092
TI Plasmid DNA vaccines are effective in the absence of IFNgamma.
AU Hassett D E; Zhang J; Whitton J L
CS Department of Neuropharmacology, CVN-9, The Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla, California 92037, USA.
NC AI-37186 (NIAID)
SO VIROLOGY, (1999 Oct 10) 263 (1) 175-83.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199911
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991126

AB Intramuscular injection of bacterially derived plasmid DNA results in the development of both humoral and cellular immune responses against plasmid-encoded antigens. **Immunostimulatory CpG** sequences within bacterial DNA are thought to enhance this process by stimulating the secretion of proinflammatory cytokines such as interferon gamma (IFNgamma) by cells of the innate immune system. Although IFNgamma induction by **CpG** elements within plasmid DNA has been documented in vitro and more recently in vivo, and coimmunization with plasmids expressing IFNgamma has been shown to enhance DNA-immunization-induced immune responses, it is unclear if IFNgamma is necessary for successful DNA immunization. To address this issue, we compared humoral and cellular immune responses in wild-type and IFNgamma-deficient mice vaccinated with a plasmid (pCMVNP) expressing the nucleoprotein gene from the arenavirus lymphocytic choriomeningitis virus (LCMV). IFNgamma-positive (BALB/c) and IFNgamma-negative (GKO) mice responded to DNA vaccination by the development of antigen-specific CD8(+) T cells, which were detectable directly ex vivo by intracellular cytokine staining and comprised 0.7-2.5% of all CD8(+) T cells in the vaccine. DNA vaccines also induced virus-specific cytotoxic T lymphocytes (CTL), even in the absence of IFNgamma. DNA vaccination of both mouse strains also was associated with a significant reduction in viral titers after LCMV challenge, indicating that, at least in the presence of other immune effector mechanisms, IFNgamma is not required for induction of protective anti-viral immunity by DNA immunization. No quantitative differences were observed in antiviral IgG levels among GKO and BALB/c vaccinees, although GKO mice did exhibit a significant reduction of the IgG2a:IgG1 ratio, in agreement with the previously documented requirement for IFNgamma in isotype switching to IgG2a. Immunized BALB/c mice produced similar levels of both IgG1 and IgG2a, indicating a mixed Th1/**Th2** response to intramuscular immunization with pCMVNP. These results show that IFNgamma induction by bacterially derived plasmid DNA does not contribute to the magnitude of the antibody response and is not required for the induction or short-term maintenance of DNA-induced CTL. However, IFNgamma is necessary for the development of IgG2a antibodies that may be crucial for protection against some pathogens.

L5 ANSWER 51 OF 63 MEDLINE DUPLICATE 28
AN 1999438257 MEDLINE
DN 99438257 PubMed ID: 10506647
TI **CpG** DNA as mucosal adjuvant.
AU McCluskie M J; Davis H L
CS Loeb Health Research Institute, 725 Parkdale Avenue, Ottawa, Canada.
SO VACCINE, (1999 Sep) 18 (3-4) 231-7.
Journal code: 8406899. ISSN: 0264-410X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991228
AB We have previously found synthetic oligodeoxynucleotides (ODN) containing **immunostimulatory CpG** motifs to be a potent adjuvant to protein administered by intramuscular injection or intranasal inhalation to BALB/c mice. Herein we have further evaluated the potential of **CpG** ODN as a mucosal adjuvant to purified hepatitis B surface antigen (HBsAg) when administered alone or with cholera toxin (CT). **CpG** ODN and CT both augmented systemic (humoral and cellular) and mucosal immune responses against HBsAg, and these could be further enhanced with higher doses of adjuvant or boosting. Overall, antibody isotypes with CT alone were predominantly IgG1 (**Th2**-like) whereas they were predominantly IgG2a (Th1-like) with **CpG** ODN alone or in combination with CT. Results from this study indicate that stimulatory **CpG** ODN are promising new adjuvants for mucosal vaccination strategies, whether used alone or in combination with other mucosal adjuvants.

L5 ANSWER 50 OF 63 MEDLINE DUPLICATE 27
AN 1999242528 MEDLINE
DN 99242528 PubMed ID: 10224473
TI DNA-Based immunization for asthma.
AU Broide D; Raz E
CS University of California San Diego, Department of Medicine, La Jolla, CA, USA.. dbroide@ucsd.edu
NC AI33977 (NIAID)
AI38425 (NIAID)
AI40682 (NIAID)
+
SO INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1999 Feb-Apr) 118 (2-4) 453-6.
Journal code: 9211652. ISSN: 1018-2438.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199906
ED Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990610
AB BACKGROUND: **Immunostimulatory** DNA sequences (ISS) containing a **CpG** motif are able to inhibit **Th2**-mediated airway eosinophilia and bronchial hyperresponsiveness in a mouse model of asthma. METHODS: To determine the optimal frequency and timing of intervention with ISS in inhibiting **Th2** cytokine production and airway eosinophilia, we used ISS administration protocols which differed in the frequency (one vs. two doses), route (systemic vs. mucosal) and timing of ISS administration (before or together with antigen) in a mouse model of ovalbumin-induced eosinophilic airway inflammation. RESULTS: ISS induced Th1 cytokine production (IFN-gamma) and effectively inhibited **Th2** cytokine production (IL-5) as well as eosinophilic inflammation when ISS was administered before or coadministered with inhaled allergen challenge. Although ISS was effective when coadministered with inhaled allergen, it was most effective when administered once 6 days prior to allergen challenge. Mucosal (intranasal and intratracheal) delivery of ISS was as effective as systemic (intraperitoneal) ISS delivery in inhibiting airway eosinophilia and switching cytokine responses from a **Th2** to a Th1 response. CONCLUSIONS: ISS is most effective in inhibiting airway eosinophilia when administered as a single dose 6 days prior to antigen inhalation. However, ISS can also significantly inhibit eosinophilic inflammation, when coadministered with antigen inhalation. Thus, ISS administered prior or together with allergen should be considered as a novel method of allergen-based immunotherapy.

L5 ANSWER 47 OF 63 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 25
AN 2000:71428 BIOSIS
DN PREV200000071428
TI **Immunostimulatory** DNA and applications to allergic disease.
AU Van Uden, John (1); Raz, Eyal
CS (1) Department of Medicine, University of California, San Diego, 9500 Gilman Dr, 128 Stein Clinical Research Bldg, La Jolla, CA USA
SO Journal of Allergy and Clinical Immunology, (Nov., 1999) Vol. 104, No. 5, pp. 902-910.
ISSN: 0091-6749.
DT General Review
LA English
SL English
AB The vertebrate immune system reacts to certain sequences of DNA with a strong TH1-inducing innate response. These sequences, termed **immunostimulatory** DNA sequences, are not fully defined but generally consist of a central nonmethylated CG dinucleotide, flanked by less highly conserved sequences (hence the alternate name **CpG** motifs). These sequences seem to be rare in vertebrates but relatively common in many lower organisms, including bacteria and viruses. It is likely that these sequences represent a danger signal to the immune system; a powerful TH1 response is induced against colocalized foreign antigen. This can be used to modify an allergic response away from a pathogenic **TH2**-dominated immune profile toward a nonpathogenic and even protective TH1 profile.

L5 ANSWER 45 OF 63 MEDLINE DUPLICATE 23
AN 2000171150 MEDLINE
DN 20171150 PubMed ID: 10705218
TI **CpG** DNA as a Th1 trigger.
AU Heeg K; Zimmermann S
CS Institute of Medical Microbiology and Hygiene, Philipps University of Marburg, Marburg, Germany.. heeg@post.med.uni-marburg.de
SO INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (2000 Feb) 121 (2) 87-97. Ref: 128
Journal code: 9211652. ISSN: 1018-2438.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 200004
ED Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000425
AB Over the last few years, it has been recognized that along with structural components and products of bacteria, bacterial DNA is also capable of signaling infectious danger to cells of the innate immune system. Particular DNA sequences (**CpG** motifs), which are abundant in prokaryotic (bacterial) but not in mammalian DNA, cause the activation and stimulation of immune cells. Research has been catalyzed by the finding that certain synthetic oligodeoxynucleotides mimic the action of bacterial DNA. **Immunostimulation** induced by bacterial DNA or synthetic oligonucleotides not only contributes to our knowledge of the pathogen-host interrelationship during infection, but can also be used therapeutically to condition or modify ongoing immune responses of the adaptive immune system. Accordingly, **CpG** motifs have been used as vaccine adjuvants as well as instructing agents to selectively induce Th1-dominated immune responses. Hence, **CpG** motifs might be used in the future as adjuvants and/or immunomodulatory agents to treat or prevent undesired **Th2**-dominated immune responses, such as allergy.

L5 ANSWER 41 OF 63 MEDLINE DUPLICATE 20
AN 2001057682 MEDLINE
DN 20484074 PubMed ID: 11027803
TI Oral, intrarectal and intranasal immunizations using **CpG** and non-**CpG** oligodeoxynucleotides as adjuvants.
AU McCluskie M J; Davis H L
CS Loeb Health Research Institute at the Ottawa Hospital, 725 Parkdale Avenue, Ottawa, Canada, K1Y 4E9.
SO VACCINE, (2000 Oct 15) 19 (4-5) 413-22.
Journal code: 8406899. ISSN: 0264-410X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001219

AB We have previously demonstrated that synthetic oligodeoxynucleotides (ODN) containing **immunostimulatory CpG** motifs (**CpG** ODN) are potent adjuvants in mice when delivered by intramuscular, intranasal and subcutaneous routes. Herein, using tetanus toxoid (TT) as a model antigen in BALB/c mice, we compared the ability of **CpG** ODN to induce mucosal and systemic humoral immune responses when antigen was delivered by three different routes: intrarectal, intranasal and oral. Results showed differences in immune responses with the three routes and also revealed that non-**CpG** "control" ODN had adjuvant effects when used at mucosal sites. This was unexpected since non-**CpG** ODN do not have such **immunostimulatory** effects in vitro or after parenteral immunization. These findings were further investigated after oral delivery of a killed influenza vaccine on its own as well as combined with TT and hepatitis B surface antigen. Our findings demonstrate that with mucosal delivery, there is a **Th2 immunostimulatory** effect associated with the phosphorothioate ODN backbone, and that the presence of **CpG** motifs shifts this towards a Th1 response.

L5 ANSWER 30 OF 63 CAPLUS COPYRIGHT 2002 ACS
AN 2001:348904 CAPLUS
DN 136:133208
TI Evaluation of **immunostimulatory** activities of human **CpG** -ODN containing 5' GTCGTT-3' motif in murine model
AU Xu, Honglin; Wang, Siqing; Wang, Shifeng; Guo, Fei; Lu, Roujian; Ruan, Li
CS Department of Viral Genetics and Immunology, Institute of Virology, Chinese Academy of Preventive Medicine, Beijing, 100052, Peop. Rep. China
SO Bingdu Xuebao (2001), 17(1), 43-47
CODEN: BIXUEA; ISSN: 1000-8721
PB Bingdu Xuebao Bianjibu
DT Journal
LA Chinese
AB The effects of synthetic human oligodeoxynucleotides (ODN) contg. unmethylated **CpG** dinucleotides (**CpG**) with specific 5'-GTCGTT-3' motif on activation of immune responses in a murine model were studied. In vitro, human **CpG**-ODN induced murine splenocyte transformation and prodn. of IgM but no IFN-.gamma.. The in vivo adjuvanticity of human **CpG**-ODN for recombinant HBsAg was examd. in mice. Human **CpG**-ODN induced a strong Th1 response with predominant IgG2a isotype. The immune response could be anchored at Th1 response when primed with human **CpG**-ODN. Boosting with human **CpG**-ODN partially reversed the **Th2** response induced by alum during priming. One dose of HBsAg with human **CpG**-ODN as adjuvant had a stronger humoral response (Th1 biased) than two doses of conventional vaccine with alum (**Th2** biased). The results showed that mice may be used as an animal model for evaluation of activities of some human **CpG**-ODN, and **CpG**-ODN contg. 5'-GTCGTT-3' motif may be a candidate adjuvant for human vaccines.

L5 ANSWER 31 OF 63 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPL

L5 ANSWER 29 OF 63 MEDLINE DUPLICATE 14
AN 2002046614 MEDLINE
DN 21622990 PubMed ID: 11750224
TI **CpG** ODN can re-direct the Th bias of established **Th2** immune responses in adult and young mice.
AU Weeratna R D; Brazolot Millan C L; McCluskie M J; Davis H L
CS Coley Pharmaceutical Canada, Ottawa, ON, Canada.. rweeratna@coleypharma.com
SO FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, (2001 Dec) 32 (1) 65-71. Journal code: 9315554. ISSN: 0928-8244.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20020124
Last Updated on STN: 20020206
Entered Medline: 20020205

AB Induction of an appropriate immune response is essential for successful immunization. For example, Th1 type immune responses are necessary for the control of intracellular infections whereas **Th2** type responses are more useful for the control of extracellular infections. **Immunostimulatory CpG** ODN (oligonucleotides containing unmethylated cytosine and guanine dinucleotides in specific base contexts) act as potent adjuvants and have been shown to induce Th1 type immune responses with a number of different antigens. This study investigates the effect of **CpG** ODN on the Th bias of immune responses generated against the hepatitis B major surface antigen (HBsAg) in adult (6-8 weeks old) and young (<1 week old) BALB/c mice. It also investigates the potential of **CpG** DNA to reverse a pre-established **Th2** response generated as an adult or as a neonate, following re-exposure to HBsAg in adult life. Both adult and young mice immunized with HBsAg/ **CpG** ODN had a Th1 biased immune response (strong cytotoxic T-lymphocyte (CTL) induction, IgG2a>>IgG1). In contrast, mice immunized with HBsAg/alum had a **Th2** type immune response (poor CTL, IgG1>>IgG2a). More importantly, when animals were immunized with HBsAg/alum and boosted with HBsAg/**CpG** ODN, the **CpG** ODN were able to re-direct the **Th2** response pre-established by alum, whereas the animals receiving the primary immunization with HBsAg/ **CpG** ODN and later boosted with HBsAg/alum maintained their Th1 bias, even after the boost with alum. These data suggest that **CpG** ODN have the ability to augment both humoral and cell mediated immune responses and override the **Th2** bias created by alum, even in very young animals, which are known to have a **Th2** biased immune system.

L5 ANSWER 19 OF 63 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:267700 BIOSIS
DN PREV200100267700
TI Parenteral and mucosal prime-boost immunization strategies in mice with hepatitis B surface antigen and **CpG** DNA.
AU McCluskie, Michael J. (1); Weeratna, Risini D. (1); Davis, Heather L. (1)
CS (1) Coley Pharmaceutical Canada, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9 Canada
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A652. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB It has previously been demonstrated that synthetic oligodeoxynucleotides (ODN), containing **immunostimulatory CpG** motifs (**CpG** ODN), are a highly effective adjuvant when delivered by parenteral (intramuscular) or mucosal (oral, intranasal, intrarectal) routes. However, there have been no studies to date using combined parenteral/mucosal approaches with **CpG** DNA as adjuvant. In this study we evaluated different parenteral (IM) prime-mucosal (IN) boost and mucosal prime-parenteral boost strategies using hepatitis B surface antigen (HBsAg) alone or with different adjuvants: aluminum hydroxide (alum), cholera toxin (CT), **CpG** ODN. In addition, since **CpG** ODN has previously been shown to act synergistically with other adjuvants after parenteral or mucosal delivery, we also evaluated adjuvant combinations: alum + **CpG** ODN, and CT + **CpG** ODN. The effects of adjuvant and administration strategy on systemic and mucosal humoral responses were measured, as well as cell-mediated immune responses including T-cell proliferation and cytotoxic T lymphocyte (CTL) activity. These results were compared to parenteral only or mucosal only strategies. Our findings demonstrate that parenteral immunization can prime for mucosal responses even when different lymph nodes were being targeted. HBsAg-specific immune responses (IgG in plasma, CTL, T-cell proliferation) induced by parenteral prime could all be significantly enhanced by mucosal boosting and despite the fact that IM immunization alone could not induce mucosal IgA, it could prime for a subsequent mucosal boost. In addition, the presence of adjuvant at time of boosting could influence the nature of subsequent immune responses (Th1 vs **Th2**). Mice primed IN could have their systemic immune responses boosted with a parenteral administration and surprisingly, it was also possible to enhance mucosal responses induced by IN prime with an IM boost. These results give an interesting insight into the understanding of immune activation by the different routes of vaccine delivery.

L5 ANSWER 17 OF 63 MEDLINE DUPLICATE 9
AN 2001409121 MEDLINE
DN 21157786 PubMed ID: 11257405
TI The potential of oligodeoxynucleotides as mucosal and parenteral adjuvants.
AU McCluskie M J; Weeratna R D; Davis H L
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SO VACCINE, (2001 Mar 21) 19 (17-19) 2657-60.
Journal code: 8406899. ISSN: 0264-410X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200107
ED Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Synthetic oligodeoxynucleotides (ODN) containing **immunostimulatory** **CpG** motifs (**CpG** ODN) are potent adjuvants in mice when delivered by parenteral (intramuscular, subcutaneous) and mucosal (intranasal, oral and intrarectal) routes. We have recently shown that with mucosal delivery non-**CpG** ODN can also have **immunostimulatory** properties which, in contrast to the Th1-bias characteristic of **CpG** ODN, are predominantly **Th2**-like. Herein, using hepatitis B surface antigen (HBsAg) and tetanus toxoid (TT) as model antigens in BALB/c mice, we have examined a number of different ODN (**CpG**, non-**CpG**, poly-T, poly-CG) to determine their effects on immune responses after mucosal (oral) and parenteral (IM) immunizations. Our findings demonstrate that with mucosal delivery, there is a **Th2**-biased **immunostimulatory** effect that is associated with non-**CpG** ODN, and that the presence of **CpG** motifs can shift this towards a Th1 response. The adjuvant effect of non-**CpG** ODN was much less evident after parenteral immunization.

L5 ANSWER 4 OF 63 MEDLINE
AN 2002385740 IN-PROCESS
DN 22129799 PubMed ID: 12133504
TI **CpG**-ODN is a potential candidate adjuvant for human vaccines.
AU Xu Honglin; Wang Shifeng; Guo Fei; Lu Roujian; Ruan Li
CS Department of Viral Genetics and Immunology, Institute of Virology, Chinese Academy of Preventive Medicine, Beijing 100052, China.
SO CHUNG-HUA I HSUEH TSA CHIH [CHINESE MEDICAL JOURNAL], (2002 Apr) 82 (8) 553-6.
Journal code: 7511141. ISSN: 0376-2491.
CY China
DT Journal; Article; (JOURNAL ARTICLE)
LA Chinese
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020723
Last Updated on STN: 20020723
AB OBJECTIVE: To evaluate the adjuvanticity of **CpG**-ODN for human vaccines in animal models. METHODS: To find suitable animal models, the human **CpG**-ODN were examined for their in vitro **immunostimulatory** activities for murine and Rhesus monkey immune cells. Then by using recombinant HBsAg as a model antigen, the adjuvanticity of human **CpG**-ODN was evaluated in the animal models. RESULTS: Rhesus monkey B cells responded well to all the human **CpG**-ODN, similarly as that of human B cells. In contrast, only the human **CpG**-ODN with the **CpG** motif 5'GTCGTT 3' (CpG2006 etc) could induce murine splenocytes to secret IgM and IFN-gamma, while those with the **CpG** motif 5'GTCGTC 3' (CpGT7 etc) had less or no effects. The results suggested that Rhesus monkeys and mice could be used as animal models to evaluate the in vivo activities of different human **CpG**-ODN. Immunized with HBsAg combined with various human **CpG**-ODN, the mice elicited a stronger Th1 humoral immunity. Consistent with the in vitro findings, **CpG**-ODN with the **CpG** motif 5'GTCGTT 3' were more potent than those with the **CpG** motif 5'GTCGTC 3'. But of note, all the sequences had the same ability for modulation of Th1/**Th2** immune response, with the ratio of IgG2a/IgG1 around 1. However, human **CpG**-ODN had less adjuvanticity for HBsAg in Rhesus monkeys; only CpGT7 increased the antibody titers by 2 times, while CpG2006 had no effect. CONCLUSION: The preliminary results derived from animal models showed that **CpG** -ODN was a potential candidate Th1 adjuvant for human vaccines.

L5 ANSWER 1 OF 63 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002153951 EMBASE
TI Role of mitogen-activated protein kinases in **CpG** DNA-mediated IL-10 and IL-12 production: Central role of extracellular signal-regulated kinase in the negative feedback loop of the **CpG** DNA-mediated Th1 response.
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SO Journal of Immunology, (1 May 2002) 168/9 (4711-4720).
Refs: 62
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB The mitogen-activated protein kinases, extracellular signal -regulated kinase (ERK), and p38, are activated in response to infectious agents and innate immune stimulators such as **CpG** DNA, and regulate the subsequent initiation and termination of immune responses. **CpG** DNA activates p38 and ERK with slightly different kinetics in monocytic cells. The present studies investigated the roles of these two key mitogen-activated protein kinases in regulating the **CpG** DNA-induced production of pro- and antiinflammatory cytokines in the macrophage-like cell line RAW264.7. p38 activity was essential for the induction of both IL-10 and IL-12 expression by **CpG** DNA. In contrast, **CpG** DNA-mediated ERK activation was shown to suppress IL-12 production, but to be essential for the **CpG** DNA-induced IL-10 production. Studies using rIL-10 and IL-10 gene-deficient mice demonstrated that the inhibitory effect of ERK on **CpG** DNA-mediated IL-12 production is indirect, due to the role of ERK in mediating IL-10 production. These results demonstrate that ERK and p38 differentially regulate the production of pro- and anti-inflammatory cytokines in APCs that have been activated by **CpG** DNA. **CpG** DNA-induced p38 activity is required for the resulting innate immune activation. In contrast, ERK plays a central negative regulatory role in the **CpG** DNA-mediated Th1 type response by promoting production of the **Th2** type cytokine, IL-10.